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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
GAMBEL,P	

ART UNIT	PAPER NUMBER
1806	30

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DATE MAILED: 09/18/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on 6/16/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims REJECTIONS WHICH STILL REMAIN AND RESPONSE TO APPLICANT'S ARGUMENTS are pending in the application.

Of the above, claims 10, 12 are withdrawn from consideration.

2. ☑ Claims 1-7 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 8, 9, 11, 13-19 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

15. Claims 1-7 have been canceled.
Claims 11, 13, 14 and 15 have been amended.
Claims 16-19 have been added.
Claims 8-19 are pending.

16. Concerning applicant's request for clarification concerning the restriction requirement, it is simply noted that applicant's elected species is CD44-specific antibodies as the agent under consideration as the elected invention.

In reviewing the comments on page 3 of the examiner's Action, mailed 2/17/95 (Paper No. 26), the examiner notes that this is the language of an election of species under 35 USC 121.

Applicant's election without traverse of Group I (anti-CD44 antibody) in Paper No. 28, filed 5/17/95 is acknowledged.

Claims 10/12 and claimed limitations drawn to Group II: soluble CD44; Group III CD44: oligopeptides and Group IV: hyaluronate have been withdrawn from consideration, as the non-elected species.

Therefore, claims 8, 9, 11 and 13-19 are under consideration.

REJECTIONS WHICH STILL REMAIN AND RESPONSE TO APPLICANT'S ARGUMENTS

17. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 26. Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes.

18. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

24. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an

enabling disclosure.

Applicant has not disclosed how to use CD44-specific antibodies therapeutically in humans. There is insufficient information or nexus of the invention with respect to the in vitro or in vivo operability of claimed therapeutic strategy to inhibit CD44-facilitated entry of HIV into cells.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs such as antibodies can be species- and model-dependent, it is not clear that reliance on the in vitro inhibition of monocyte infection by a particular HIV strain accurately reflects the relative of the claimed therapeutic strategy.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

It has been well known in the art that retroviral infections in general, and HIV infections, in particular, are refractory to anti-viral therapies. Further, it has been well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Further, as taught by Fahey et al. (Clin. Exp. Immunol., 1992), clinical trials monoclonal antibodies therapies have not provided any clinical benefits and "it is not clear how adding these additional antibodies would make a difference (see page 3, column 2, paragraph 3). Similarly, Hirsch et al. (N. Eng. J. Med., 1993) clearly teach that the success of translating [promising avenues of investigation into clinical practice has been meager (Page 1806, column 1, paragraph 2). For example, while soluble CD4 is a potent inhibitor of finding of certain strains of HIV-1 to CD4 cells in vitro, clinical HIV-1 isolates are less susceptible to such inhibition (page 1691, column 1, paragraph 2). Therefore, the art does recognize the benefit of even HIV-specific or CD4-specific (versus claimed CD44-specific) inhibitors can block HIV infection clinically.

Furthermore, it is noted that Rivaderneira et al. teach CD44-specific antibodies could inhibit the monocytotropic HIV-1-BaL infectivity of monocytic cells to some degree under certain culture conditions but could not block lymphocytotropic HIV-1 infection (manuscript filed with the 12/23/93 amendment, Paper No. 18). Guo et al. also teach anti-CD44 antibodies did not inhibit infection (J. Immunol., 1993; see entire document, particularly page 2234, column 2, paragraph 1).

The claimed method utilizing CD44-specific antibodies appears limited to monocytic cells (versus lymphocytes) and does not completely inhibit infection of one HIV isolate in these cells under defined culture conditions. Therefore, it is not clear how the CD44-specific antibodies could inhibit HIV infection by various HIV strains in mixed leukocyte populations either in vitro or in vivo.

Concerning antibody therapy, Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3)(Tibtech, 1993). Humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies will contain unique amino acid sequences.

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4). The inherent difficulties of this approach include development of serum sickness after injection of foreign protein, diminishing therapeutic effects after prolonged therapy and the potential for promotion of infection. In a brief review of adhesion therapy, Shaffer relays such concerns about monoclonal antibodies, which are promising but involve toxicities and do not seem to have a lasting effect upon repeated use (Biotechnology Newswatch, 1993).

In the absence of clear and convincing evidence commensurate in scope with the allegations and claims, applicant has not provided convincing evidence that their claimed invention is effective as a therapeutic or preventative for HIV infection based on the in vitro inhibition of HIV infection of monocytes in vitro alone.

Such allegations are not found convincing. Therefore, applicant has not provided sufficient information or nexus information a priori that establishes the efficacy of the claimed invention for the treatment of human disease.

Applicant's arguments, filed 5/17/95 (Paper No. 28), have been fully considered but are not found convincing.

Applicant argues, in part, that since a previous rejection under 35 U.S.C. § 101 has been withdrawn, the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn. Applicant is reminded that factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Both the examiner and the applicant agree that the instant application has demonstrated the ability of CD44-specific antibodies to inhibit HIV infection of mononuclear phagocytes in vitro. However, the examiner and the applicant disagree whether this would be predictive of the ability of CD44-specific antibodies to inhibit HIV infection of any susceptible cell in vitro and in vivo. It is not an issue of 100% effectiveness, as argued by applicant. It is noted that applicant asserts the skilled artisan would appreciated that in vivo and ex vivo treatments would be appropriate. Also, applicant asserts CD44-specific antibodies would be appropriate in the prevention of any susceptible host cell including blood.

It has been well known in the art that cellular CD4 has been recognized as the predominant membrane protein that interacts with HIV. However, it has been well known that HIV infection occurs in cells that express variable or no detectable levels of CD4. It has been well known that $CD4^+$ T cells are the primary target of HIV infection both in vitro and in vivo. Therefore, it would not have been predictable that targeting CD44 in mononuclear phagocytes would affect HIV infection of any susceptible cell either in vitro or in vivo. For example, either the individual or the blood would be infected by HIV via CD4, irregardless of blocking CD44 infectivity of mononuclear phagocytes. Further, it is noted that CD44-specific antibodies can block HIV infection of mononuclear phagocytes in vitro, however these same antibodies can not block the infection of mitogen-stimulated lymphocytes or cells of a T lymphocyte line in vitro (Rivadeneira et al., Aids Research and Human Retroviruses, 1995; see entire document including Abstract). Therefore applicant's assertions do not appear consistent with applicant's own observations.

Appellant's assertions also run contrary to current understanding of the lack of predictability of HIV treatments as well as that at the time the invention was made as acknowledged in Ex parte Balzarini 21 USPQ2d 1892 (1991), which stated that skilled persons and the evidence of record supports the conclusion that in vitro testing of anti-viral compounds is not in and of itself predictive of in vivo efficacy in the treatment of retroviral diseases broadly or specifically AIDS (page 1896, column 2, paragraph 2).

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective HIV-specific/adhesion-based/antibody-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting HIV infection in vivo or to all cells. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

Applicant's arguments have not been found persuasive and the rejection is maintained. It is noted that if applicant limits claims to the in vitro inhibition of HIV infection of mononuclear phagocytes or monocytes, then the rejection under 35 U.S.C. § 112, first paragraph would be withdrawn. Applicant should note that claims drawn to "ex vivo" are rejected with respect to new matter, as set forth in section below.

Claims 8, 9, 11, 13-19 stand rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

25. The specification is objected to and claim 11 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) sequenced; or (3) deposited.

It unclear if a cell line which produces an antibody having the exact structural and chemical identity of A1G3 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not

be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species A1G3. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

In addition, the identifying information set forth in 37 CFR 1.809 (d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Applicant's arguments have been fully considered.

The previous objection/rejection for the deposit of the A3D8 antibody has been withdrawn in response its public/commercial availability. Although applicant did not provide evidence of this, the examiner has determined this availability from Sigma Chemical Company (see Catalog 1992, page 1119).

However no such evidence of public availability or assurances have been provided for the A1G3 antibody/hybridoma. Therefore, applicant's arguments concerning the enablement and public availability of the A1G3 antibody are not found convincing in the absence of evidence to the contrary. For the reasons of record, the rejection of claim 11, drawn to the A1G3 antibody is maintained.

26. Claim 11 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is indefinite in the recitation of "A1G3" because their characteristics are not known. The use of "A1G3" monoclonal antibodies as the sole means of identifying the claimed antibodies renders the claim indefinite because these terms are merely laboratory designations which do not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely distinct cell lines or hybridomas.

The amendments must be supported by the specification so as not to add any new matter.

Applicant's arguments have been fully considered. As indicated above in section 25, the previous rejection concerning the A3D8 antibody has been withdrawn, however it remains unclear whether the A1G3 antibody has satisfied the rejection under 35 U.S.C. § 112, first paragraph and, in turn, the laboratory designation would be indefinite for the reasons of record. Since there is no evidence of a deposit or public availability, the laboratory designation would not necessarily reflect a CD44-specific antibody with the exact characteristics required by the claimed invention. The rejection is maintained with respect to the recitation of A1G3 in claim 11.

27. The previous rejection of claims 8, 9, 11, 13-15 under 35 U.S.C. § 103 as being unpatentable over Willerford et al. (J. Immunol., 1990) or Landay (U.S. Patent No. 5,108,904) in view of Nicholson et al. (J. Immunol., 1986) and Matsushita et al. (AIDS Res. Hum. Retrovir., 1990) have been withdrawn in response to applicant's arguments and amended claims, filed 5/17/95 (Paper No. 28). Similarly, newly added claims 16-19 are free of the prior art concerning the use of CD44-specific agents particularly antibodies to inhibit HIV infection.

Applicant clearly states that the instant invention is not drawn to the use of CD44-specific immunotoxins and that the current claimed recitation supports this conclusion.

NEW REJECTIONS BASED UPON APPLICANT'S AMENDMENT

28. The amendment filed 5/17/95 (Paper No. 28) is objected to under 35 U.S.C. § 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: There appears to be no written description of the terms "mucosal cells" or "ex vivo" as now claimed in claims 17 and 19. Although applicant's amendment directs the examiner to page 30 of the specification for this support, these terms do not appear in the specification as indicated by applicant's amendment nor do they appear in the specification, as filed. Applicant is reminded that new matter is a written description issue.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed does not provide support for the invention as is now claimed. Claims 17 and 19 are rejected for the use of terms of "mucosal cells" and "ex vivo" because there appears to be no written description of these terms, as originally filed.

Applicant is required to cancel the new matter in the response to this Office action.

29. No claim is allowed.

It is noted that claims drawn to methods of inhibiting HIV infection of mononuclear phagocytes in vitro with CD44-specific antibodies would be considered allowable.

30. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

31. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Margaret Parr can be reached on (703) 308-2454. The fax phone number for Group 180 is (703) 305-3014 or (703) 308-4227. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
September 15, 1995

M. Parr 9/18/95
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